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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,350	01/27/2006	Tetsuro Tateishi	KUZ0028USNP	2515

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EXAMINER	
PURDY, KYLE A	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
05/10/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/566,350	TATEISHI ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,11,20 and 22-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 6, 11, 20 and 22-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The Examiner acknowledges receipt of the amendments filed on 02/04/2010 wherein claims 1, 11, 22-26, 28 and 29 has been amended and claims 8, 9 and 21 have been cancelled.

2. Claims 1, 5, 6, 11, 20 and 22-31 are presented for examination on the merits. The following rejections are made.

Response to Amendment

3. The declaration under 37 CFR 1.132 filed 02/04/2010 is insufficient to overcome the rejection of claims 1, 5, 6, 11, 20 and 22-31 based upon Modiamo et al. (1998) in view of Hirano et al. (US 6495159) and Higo et al. (US 5866157), evidenced by Walters (1989) as set forth in the last Office action.

4. Applicants declaration provides data showing that a combination of acetic acid and isopropyl myristate results in greater skin penetration than acetic acid and oleyl alcohol and acetic acid and isosteearyl alcohol.

5. This showing is not persuasive. All of these penetration enhancers were known in the art and each were suggested to be combined with the other. Modiamo specially suggests using penetration enhancers to provide a penetration enhancing benefit to bisprolol. Higo teaches that matrix patch formulations may comprise transdermal penetration enhancers selected from both organic acids and isopropyl myristate. An exemplified organic acid is sodium acetate (see column 3, lines 10 and column 5, line 15). Thus, any ordinary person would have been motivated to produce a transdermal enhancing composition comprising both acetic acid (sodium salt) and isopropyl myrisate. Thus, Applicants invention would have been obvious in view of the prior art.

Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of obviousness. Newell Cos. v. Kenney Mfg. Co., 864 F.2d 757, 769, 9 USPQ2d 1417, 1427 (Fed. Cir. 1988). With respect to the improved penetration benefit over the other combinations, this would have been a property of this obvious combination. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of an obvious composition. However, the discovery of a previously unappreciated property of a prior art composition (i.e. improved transdermal benefit) does not render that obvious composition patentably new to the discoverer.

Response to Applicants' Arguments

6. Applicants arguments filed 02/04/2010 regarding the rejection of claims 21, 22, 24, 26 and 29 made by the Examiner under 35 USC 112, first paragraph (new matter) have been fully considered and they are found persuasive. This rejection has been overcome by amendment to the claims. It's noted that claims 21 has been cancelled.

7. Applicants arguments filed 02/04/2010 regarding the rejection of claims 8, 9 and 21 made by the Examiner under 35 USC 103(a) over Modiamo et al. (1998) in view of Hirano et al. (US 6495159) and Higo et al. (US 5866157), evidenced by Walters (1989) have been fully considered and they are found persuasive. This rejection has been overcome by amendment to the claims.

8. Applicants arguments filed 02/04/2010 regarding the rejection of claims 1, 5, 6, 11, 20 and 22-31 made by the Examiner under 35 USC 103(a) over Modiamo et al. (1998) in view of Hirano et al. (US 6495159) and Higo et al. (US 5866157), evidenced by Walters (1989) have been fully considered but they are not found persuasive.

9. The rejection of claims 1, 5, 6, 11, 20 and 22-31 made by the examiner under 35 USC 103(a) is **MAINTAINED** for the reasons of record in the office action mailed on 10/09/2009.

10. In regards to the 103(a) rejection, Applicant asserts the following:

A) None of the references teach using both sodium acetate and isopropyl myristate together; and

B) Heller is directed to pindolol and propranolol, not bisprolol.

11. In response to A, while no reference discloses that exact combination, Higo does suggest it. Higo, at column 3, line 10, states that the sodium acetate may be used for its penetration enhancing benefit. Column 5, line 15 teaches that isopropyl myristate may also be used as a penetration enhancer. Thus, any ordinary person would recognize that both, being useful for the same purpose, could be combined together with a reasonable expectation that that new composition would also have similar properties. Thus, if one were to combine both sodium acetate and isopropyl myrsitate, it would have been a product of ordinary skill and common sense, not one of innovation.

12. In response to B, it is acknowledged that Heller is directed to pindolol and propranolol, not bisprolol. It's noted that pindolol, propranolol and bisprolol are all similar species in that they have a common structural feature and are all used as beta-blockers. Heller shows that penetration enhancers substantially increase the skin penetration rate of pindolol and propranolol. Thus, an ordinary person would expect penetration enhancers to also be capable of increasing the penetration rate of bisprolol, just as they increase the skin penetration rate of it's structural relatives.

Maintained Rejections, of Record
Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. **Claims 1, 5, 6, 11, 20 and 22-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Modamio et al. (International Journal of Pharmaceutics, 1998, 173, 141-148; of record) in view of Hirano et al. (US 6495159; of record), Higo et al. (US 5866157; of record) and Heller et al. (US 4710497; published 12/01/1987), further evidenced by Walters (Transdermal Drug Delivery, 1989, New York, NY, pp. 197-246; of record).**

15. Modiamo is a study pertaining to the penetration rate of bisoprolol fumarate across a section of human skin. It is taught that bisoprolol is a beta-blocker, and that research is underway to develop transdermal patches for the efficient delivery of beta-blockers such as bisoprolol (and celiprolol) for patients who cannot take medicines by themselves or when oral administration of such drugs may be inadvisable due to unpleasant side effects (see page 142, column 1, 1st paragraph; see instant claim 1). It is taught that the drug is applied to a surface area of 16 cm^2 (see page 144, column 2, 3rd paragraph) wherein the drug possesses a penetration rate of 1.19±060 $\mu g/hr/cm^2$ (see abstract). Modamios experiments indicate that bisoprolol has a difficult time crossing the skin barrier, and the theoretical plasma concentration provided by the system is well below bisoprolols therapeutic concentration (see abstract). It is stated that in order to for the bisoprolol containing patch to be therapeutically effective, transdermal absorption enhancers are

required to improve bisoprolols diffusion properties (see abstract and page 147, first column, third paragraph). Modamio incorporates by reference the teaching of Walters to illustrate typical absorption enhancers which include solvents like water and lower alcohols, surfactants such as fatty acids and fatty alcohols, and other chemicals such as urea (see pages 203-227).

16. Modamo fails to teach the patch that possesses a matrix type adhesive layer, wherein the adhesive layer comprises a carboxyl group such as that of 2-ethylhexyl acrylate-butyl acrylate-acrylic acid copolymer. The teaching of Modamio fails to teach the rate of penetration of bisoprolol through the skin as 4.0-300 $\mu g/hr/cm^2$. Modamio also fails to specifically teach the absorption promoters as being for example, lauryl alcohol, an organic acid or isopropyl myristate.

17. Hirano is drawn to a percutaneous treatment device that possesses a pressure-sensitive adhesive acrylic polymer layer that allows for the controlled release of a medicine (see column 1, lines 9-10). The acrylic adhesive taught by Hirano may be a copolymer of (meth)acrylic acid alkyl ester monomers and other functional monomers (see column 6, lines 25-31). The (meth)acrylic acid alkyl ester monomers include butyl acrylate, 2-ethylhexyl acrylate, and 2-ethylhexyl methacrylate (see instant claims 1-3, 13, 15, 17, and 19). The functional monomer is said to be a monomer having a carboxylic acid such as acrylic acid, methacrylic acid (see column 6, lines 47-51; see instant claim 1). Furthermore, it is taught in Example 1 and 2 that vinyl acetate may be implemented as a monomer in the copolymer (see instant claim 1). For example, it is present in the copolymer of 2-ethylhexyl acrylate/ethylacrylate/vinyl acetate copolymer (see Example 2). Moreover, the idea of combining an acrylic copolymer with an elastomeric polymer is expressly taught at column 5, lines 43 to line 6 column 3. Specifically, Hirano discloses the

use of polyisobutylene (available from Exxon chemical as trade name "Vistanex") and styrene-isoprene-styrene copolymer (available from Japan Synthetic Rubber Co. as "JSR 5000") (see instant claim 1). The reference also teaches the use of aliphatic acids, aliphatic alcohols and esters of aliphatic acids having 7-20 carbon atoms as absorption promoters (see column 4, lines 42-56; see instant claims 8-9). Some specific examples of disclosed absorption promoters include lauryl and myristyl alcohol and they may be used in an amount of 0.1-10% by weight. Further, Hirano teaches their patch (see abstract and Figure 1) possesses a backing layer (i.e. drug permeable membrane) which is in direct contact with the adhesive layer (see instant claim 20).

18. Higo is drawn to a matrix patch formulation which comprises an adhesive layer containing a physiological active substance, an organic acid, a hydrophobic material, a tackifying resin, a plasticizer and an absorption enhancer (see abstract). The absorption enhancers (and organic acids) are included in the formulations taught by Higo in order to allow for sufficient uptake of physiological active material from the skin by improving the transdermal mobility for said active substances (see column 1, lines 35-40). Absorption enhancers taught by Higo include organic acids such as sodium acetate (see column 2, lines 62-66 and column 3, lines 12-19) which is to be used in an amount of 0.01-15% by weight, as well as isopropyl myristate which is to be used in an mount of between 0.1-20% by weight (see column 5, line 11; see instant claims 23 and 26).

19. Heller is directed to methods of percutaneously administering physiological agents to the skin. Examples 40 and 41 are to determining the rate of penetration of the beta-blocker pindolol with different absorption enhancers. Using isopropyl myristate the rate ranged from 14.6 up to

98.1 μg/hr/cm^2 (see instant claims 1, 21 and 22). It's taught that the absorption promoters are to be used in an mount of between 0.01-50% by weight of the composition (see column 9).

20. Thus, it would have been obvious to one of ordinary skill, at the time the invention was made to combine the references of Modamio, Hirano, Higo and Heller because in doing so would result in a transdermal matrix type patch that possesses improved adhesive properties while allowing for the modulated release (and improved absorption properties) of the active substance, bisoprolol. The significance of Modamio is that the reference suggests using a transdermal patch for the delivery of bisoprolol. Albeit true that Modiamo fails to teach a transdermal patch explicitly, Modiamo does states that the transdermal pathway is of interest for the administration of the drugs being studied. Such a recitation would motivate any ordinarily skilled artesian to look to the art so as to identify a structure capable of supporting such a transdermal delivery system. With respect to the penetration rate of bisoprolol, it is also noted that the value disclosed by Modiamo is below the instantly claimed values. However, Modiamo teaches that this rate could be substantially improved by adding various absorption enhancers. Higo, Hirano and Heller each teach using penetration enhancers in their compositions to aid in the penetration rate of bisoprolol. In fact Heller uses isopropyl myristate with a beta-blocker and achieves rates of penetration between 14.6 up to 98.1 μg/hr/cm^2. As Modiamo suggests that penetration enhancers would have to be added to the transdermal delivery system to improve the drugs percutaneous absorption properties, one would have looked to other transdermal delivery systems for delivery of similar agents. If such a result was the finding that a delivery rate of 98.1 μg/hr/cm^2 resulted in a pharmacologically useful plasma bisoprolol concentration, then this would have been a product of common sense and ordinary skill in the art. The instantly claimed

amounts of absorption enhancer are also suggested by Higo, Hirano and Heller. Each of these teachings suggests using the absorption enhancer in an amount as instantly claimed. With respect to the use of 2-ethylhexyl acrylate/acrylic acid/vinyl acetate copolymer, this is obvious. First, the notion of implementing an acrylic adhesive layer for the delivery of bisoprolol is obvious because one would want the patch to be capable of effectively adhering to the skin for constant delivery of the substance. Second, the teaching of Hirano teaches an array of monomers to be used in the synthesis of copolymers which include 2-ethylhexyl acrylate, acrylic acid and vinyl acetate. It would have been obvious to copolymerize these monomers as it stated by Hirano that the adhesive copolymer preferably contains monomers having the aforementioned chemical names. Reading from a list and selecting from disclosed compounds, in this case acrylic monomers, is no more ingenious than selecting the last piece to put in the last opening of a jigsaw puzzle. See MPEP 2144.07. Therefore, a matrix patch capable of delivering bisoprolol is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

22. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/
Examiner, Art Unit 1611
May 3, 2010

/David J Blanchard/
Primary Examiner, Art Unit 1643